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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,204	07/18/2001	Avi Ashkenazi	10466/118	1632

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	16

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,204	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46 and 49-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46 and 49-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 2/19/03 has been entered.

Response to Arguments

The rejections of claims 47 and 48 are moot in view of the cancellation of the claims.

The rejection of claims 39-44 and dependent claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims. Note that claims 52 and 53 remain rejected.

The rejection of claims 39-43 and 52-58 under 35 USC 112, first paragraph, for insufficient written description is withdrawn in view of the amendment to the claims.

The rejection of claims 52-54 under 35 USC 102(b) as anticipated by US Patent 5,695,995, is withdrawn in view of the amendment to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

The declaration under 37 CFR 1.132 filed February 19, 2003, is insufficient to overcome the rejection of claims 39-46 and 49-58 based upon 35 USC 101 and 112, first paragraph, as set forth in the last Office action because: While the declaration and accompanying references show that "real-time PCR" is a reliable means of determining gene copy number in cells or tissues, there are utility and enablement issues of aneuploidy and antibody *vs.* DNA not resolved by the declaration that require the rejection to be maintained. The utility and enablement for claims 39-44 are further discussed under the appropriate section for the rejections below.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 52 and 53 and dependent claim 54 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous Office action (paper #11, p. 3, lines 9-20), and for the following reasons addressing the amendment to the claims: The instant specification presents examples but not a limiting definition of

"moderately stringent conditions" or "high stringency conditions" (p. 74, lines 5-22). The conditions are exemplified in the specification and "**may be** identified as described by Sambrook et al." (emphasis added by Examiner). However, there is no one specific condition or limiting range of conditions presented in the specification or pointed to in Sambrook, which is not properly incorporated by reference if the material therein is essential to the claimed invention.

Claims 52 and 53 remain indefinite because the metes and bounds of the claims are not clear due to the use of the terms related to hybridization conditions.

Applicants argue that "As noted by the Examiner, these stringency conditions are disclosed in the specification. In particular, moderately stringent conditions and high stringency conditions are defined, for example, at page 74, lines 4 *et seq.*" The argument has been fully considered, but is not persuasive. As stated in the previous Office action and discussed above, the Examiner noted that the specification presents only examples without a limiting definition of the named stringency conditions. As a result, the skilled artisan cannot know what particular condition or restricted range of conditions are intended to circumscribe the nucleic acids being claimed.

Claim Rejections - 35 USC § 101

Claims 39-46 and 49-58 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action (paper #11) on pages 3-5 and for the following reasons addressing the amendment to the claims: While independent claims have been amended to recite that "said isolated nucleic acid encodes a polypeptide associated with the formation or growth of lung or colon tumor", this utility is not a specific and substantial asserted utility. The reasons are discussed below in response to Applicants' arguments.

Applicants argue the gene amplification data in the present application are sufficient to establish utility of the nucleic acid encoding PRO339 polypeptide because such amplification is "an essential mechanism for oncogene activation", occurs in most solid tumors, and PRO339 showed 2 to 3 fold gene amplification in some lung and colon tumors. The argument has been fully considered, but is not persuasive. Even though in some circumstances and as discussed in the declaration, TaqMan™ real-time PCR can accurately and reproducibly assess gene

amplification, in cancerous tissues it is necessary to account for the possibility of aneuploidy. This was discussed in the previous Office action on page 4, lines 17-21. Sen et al. (Curr. Opin. Oncol., 2000, previously cited) begins by saying "Numeric aberrations in chromosomes, referred to as aneuploidy, is commonly observed in human cancer." Therefore, because the gene amplification observed for PRO339 is small and could reasonably be expected to be due to aneuploidy, the implicit utility of a lung or colon tumor diagnostic is not specific and substantial.

Applicants argue that the number and type of normal tissues used as controls was stated in the specification. The Examiner thanks Applicants for pointing out the data for the normal control, which is the genomic DNA from 10 normal healthy individuals.

Applicants argue that the asserted utility, particularly in view of the Goddard Declaration, is credible. This is a credible utility, if indeed the nucleic acid could be used for the asserted utility. However, as discussed above, because aneuploidy has not been accounted for, it cannot be concluded that the claimed invention is useful as a diagnostic marker for colon or lung cancer because it has not been shown to be substantial and specific.

Applicants argue and the amended claims state that the encoded polypeptide is associated with the formation or growth of lung or colon tumor. The argument has been fully considered, but is not persuasive. Assuming the DNA had utility as a lung and colon tumor marker, which it does not as discussed in the previous Office action and above, the encoded protein would not have utility because it is not known what the protein does or if the level of PRO339 protein in tumors corresponds to nucleic acid transcript level, *i.e.*, if an increased gene amplification in lung and colon tumors corresponds to an increased amount of expressed protein. It does not necessary follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95, p.14722, second paragraph; Exhibit D of the declaration) teaches that:

> An analysis of WISP-1 gene amplification and expression in human coon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient.

Additionally, Hayes et al. (Electrophoresis 19 :1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, because it cannot be concluded that the PRO339 is associated with formation or growth of lung or colon tumor or is useful as a diagnostic marker for colon or lung cancer, the encoded protein does not have utility. Significant further research would be required to find out what the protein does and if and how it is linked to lung and/or colon cancer.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 39-46 and 49-58 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, and for the reasons set forth in the previous Office action (paper #11) on page 6, lines 4-11, and for the following reasons addressing the amendment to the claims: While independent claims have been amended to recite that "said isolated nucleic acid encodes a polypeptide associated with the formation or growth of lung or colon tumor", it remains that one skilled in the art would not know how to use the claimed invention for the reasons discussed above.

Applicants argue that a substantial, specific and credible utility for antibodies that bind PRO339 polypeptide has been shown as discussed for the preceding 35 USC 101 rejection, so that it would not require undue experimentation to use the claimed invention. The argument has been fully considered, but is not persuasive. For reasons set forth in the previous Office action and as discussed addressing the 1.132 declaration and rejection under 35 USC 101 above, namely lack of accounting for aneuploidy in cancer cells and the lack of associate of the encoded protein with a specific diagnostic use in view of the lack of reasonable expectation of copy number reflecting amount of expressed protein, it is maintained that it would require undue experimentation to use the claimed invention.

Applicants argue that the Examiner has named no particular reasons why the specification would not be enabling for how to use. The argument has been fully considered, but is not persuasive. As stated in the previous Office action on p. 6, lines 8-11, "The specification provides little beyond structural data and potential activities of the PRO339 polypeptide without guidance about which specific activities one could reasonable expect the polypeptide of encoding nucleic acid to possess as discussed above [under 35 USC 101]."

Claim Rejections - 35 USC § 102 and 103

Claims 39-44, 49 and 52-58 remain rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. AB037823 as evidenced by Stratagene Cloning Systems catolog (1994) for the reasons set forth in the previous Office action (paper#11, p. 8).

Claim 46 remains rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. AB037823 in view of Applicants' Admission on p. 34, lines 5-6, and Fleming et al. (Dev., 124:2973-81, 1997) for the reasons set forth in the previous Office action (paper#11, p. 9).

Applicants argue that for both the 35 USC 102 and 103 rejection, the instant application receives an effective filing date of 2/11/2000 due to the utility supported by gene amplification data; therefore, GenBank Accession No. AB037823 is not available as prior art. The argument has been fully considered, but is not persuasive. Because of the reasons discussed above for the rejections of 35 USC 101 and 112, 1st paragraph, the claimed invention lacks utility. It is maintained that effective filing date is 07/11/2001.

Note that the evidence of record requires that the rejection under 35 USC 101/112 be maintained (see above) since there is no reasonable expectation that the claimed compounds actually have the property recited in the amended claims. However, should evidence be presented that shows that the compounds do, indeed, have the required activity, it is well known that a compound and its properties are inseparable (*In re Papesch* 137 USP# 43 (CCPA 1963) 52). Therefore, the compounds are still disclosed by the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicants or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

April 30, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER